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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,324	04/19/2006	Tadayuki Imanaka	490051.401USPC	4748

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EXAMINER	
VOGEL, NANCY TREPTOW	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,324	IMANAKA ET AL.	
	Examiner	Art Unit	
	NANCY VOGEL	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 52-56* is/are pending in the application.

4a) Of the above claim(s) *52-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/21/08, 2/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 and 52-56 are pending in the case.

Information Disclosure Statement

Receipt of Information Disclosure Statements on 2/2/8/05 and 5/21/08 is acknowledged.

The information disclosure statement filed 2/28/05 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the Information Disclosure Statement is unsigned. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Election/Restrictions

Applicant's election of Group I, claims 1-7 in the reply filed on 9/17/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 52-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/17/08.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of targeted-disruption of an arbitrary gene in the genome of Thermococcus kodakaraensis KOD1, does not reasonably provide enablement for the method of targeted-disruption of an arbitrary gene in the genome of an living organism, in which the information of the entire sequence of the genome of the living organism is provided. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity

of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention: The nature of the invention is a method of targeted disruption of an arbitrary gene in the genome of a living organism, in which the entire sequence of the genome of the living organism is obtained.

The state of the prior art: At the time of the filing of the application, the nucleotide sequence of several, but not all, living organisms were known. Considerable experimentation was needed to obtain the nucleotide sequence of any particular organism.

Level of predictability in the art: It was known in the art that considerable unpredictable difficulties could be encountered during the process of obtaining the entire sequence of any particular organism. For instance, in the lecture set forth at the website www.stat.berkeley.edu/users/hhuang/STAT141/STATC141-lectureV.1.pdf (accessed 12/17/08), it is disclosed that :

"The sequence of some spans of DNA is difficult to generate. This can be because of a biased base content (this can result in failure to be cloned, poor stability in the chosen host-vector system, or inability of the polymerase to reliably copy the sequence). For example AT-rich DNA clones poorly in bacteria. GC rich DNA is difficult to sequence and often requires the use of inosine substitution for G in the reactions, and careful monitoring sequencing gel conditions.

The presence of poisonous sequence: sequence that interferes with the biology of the host organism. This could be an operator that reduced effective concentrations of

an essential DNA binding regulator, or an open reading frame that expresses a toxic protein. These problems are commoner for bacterial genomes cloned in bacterial vector-host systems, but can affect eukaryotic cloning too. The presence of repetitive DNA can result in deletion of sequences from the clone, particularly in bacterial systems, and thus the sequenced DNA will no correspond to the situation in the original source organism."

Furthermore, Wendl et al. (Bioinformatics, 20, 10, 2004, 1527-1534) states that there are assembly difficulties for repeat-rich genomes, and that bias and coverage anomalies are also important when repeats are sparse. Wendl states that "[s]uch factors cannot be readily characterized a priori" (page 1527). Therefore, the art discloses that there is significant unpredictability in the method of obtaining the entire sequence of a genome.

The existence of working examples: The specification discloses obtaining of the sequence of the genome of Thermococcus kodakaraensis KOD1.

The breadth of claims: The claims are very broad since they encompass the step of obtaining the complete nucleotide sequence of any genome of any living organism.

The amount of guidance provided: The amount of guidance regarding obtaining the complete nucleotide sequence of any and all genomes of all living organisms is limited, since the application only discloses the genome sequence of one organism, i.e. T. kodakaraensis KOD1.

The amount of experimentation needed to make or use the invention: The amount of experimentation needed to practice the invention is large, since it would require obtaining the complete nucleotide sequence of a genome of a living organism which may not be known in the art, a project which may take years and may involve significant unpredictability and experimentation.

Therefore, the claims should limited to a method for disruption of a gene in the genome of living organisms whose entire sequence of the genome were disclosed in the art at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is vague and indefinite since it is dependent on claim 5. Therefore it cannot be determined what the intended subject matter is.

Claim 5 and 6 are vague and indefinite in the recitation of “the marker gene is located in the selected region”, since the “selected region" is recited in claim 1 to be present on the genome (chromosome) of the living organism, but the claim 1 recites that the marker is present on the vector. Therefore it is unclear what is intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Imanaka et al. (Abst. Gen. Mtg. Amer. Soc. Microbiol., 103:I-115, May 18-22, 2003).

Imanaka disclose a method for target disruption of an arbitrary gene in the genome of a living organism which is Thermococcus kodakaraensis KOD1, comprising selecting at least one arbitrary region of the sequence (the target gene), providing a vector comprising a sequence complementary to the select region and a marker gene, transforming the living organism with the vector, and placing the living organism in a condition allowing homologous recombination. The region comprises at least two regions, since the region has more than one nucleotide, each of which may be considered to be a "region". The vector comprises a promoter and the method comprises a step of detecting expression product of the marker gene. There is a marker present inside of the selected region which is complementary to the selected region . The reference also discloses obtaining the genome sequence of T. kodakaraensis KOD1.

This reference contains authors in addition to the inventors named in the instant application and therefore constitutes disclosed by "another". In addition, Applicant cannot rely upon the foreign priority papers to overcome this rejection because a

translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zyskind et al. (US Patent 6,720,139) or Link et al. (J. Bact. 179:6228- 6237, 1997) in view of Blattner et al. (Science 277(5331): 1453-1474, 1997).

Zyskind et al. or Link et al. each disclose a method for target disruption of an arbitrary gene in the genome of a living organism comprising selecting at least one arbitrary region of the sequence (the target gene), providing a vector comprising a

sequence complementary to the select region and a marker gene, transforming the living organism with the vector, and placing the living organism in a condition allowing homologous recombination. The region comprises at least two regions, since the region has more than one nucleotide, each of which may be considered to be a “region”. The vector comprises a promoter and the method comprises a step of detecting expression product of the marker gene. There is a marker present outside of the selected region which is complementary to the selected region (see col. 13 line 63 – col. 15 of Zyskind; see abstract and Fig. 1 of Link). Link et al. also disclose the method in which a marker is present with the sequence that is complementary to the selected region (see Fig. 1A). The difference between the reference and the instant claims is that the reference does not disclose the step of "providing information of the entire sequence of the genome of the living organism”. However, discloses the information of the entire sequence of E. coli. It would have been obvious to one of ordinary skill in the art to have modified the method of Zyskind et al. by using the information of the sequence of E. coli in order to insert or disrupt a gene of choice, by obtaining information of the sequence close to said gene in the genome. One would have been motivated to so by the well known usefulness of the information concerning the sequence of the genome of the organism which is being manipulated, which includes the ability to accurately make alterations to regions of interest using standard genetic engineering techniques such as those disclosed by Zyskind et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
12/18/08